REMARKS

Claims 57, 59-61, 64, 66-68, 71, and 76-80 are now pending in this application. Claims 58, 62-63, 65, 69-70, and 72-75 have been canceled through this Amendment. New claims 76-80 have been added in this Amendment. Support for claims 76-80 is found in the specification as filed, specifically in Example 38, beginning on page 236, line 35, of the specification. Applicant requests consideration of the remarks below as they pertain to the specification and pending claims.

Amendments to the Specification

The specification has been amended to change the effective filing date of the application to October 10, 1995. Specifically, the Cross-Reference to Related Application section has been amended to recite that this application is a continuation of U.S. Serial Number 08/758,417 filed December 2, 1996, now U.S. Patent No. 6,300,129, which is a continuation-in-part of U.S. Serial Number 08/728,463 filed October 10, 1996, which is a continuation-in-part of U.S. Serial No. 08/544,404 filed October 10, 1995, now U.S. Patent No. 5,770,429. MPEP §201.11 (III) (G).

Amendments to the Claims

Claim 57 has been amended to recite a transgenic mouse comprising in its genome a human kappa light chain immunoglobulin transgene, where the transgene contains five human light chain Vκ segments, a plurality of human light chain Jκ segments, and a human light chain Cκ segment, which segments are operably linked to transcription regulatory sequences and undergo rearrangement in B lymphocytes *in vivo* to produce a repertoire of rearranged transgenes encoding a plurality of human kappa light chain polypeptides, which human kappa light chain polypeptides are produced in the transgenic mouse. Support for the amendments to claim 57 can be found in Example 38, beginning on page 236, line 35, of the specification.

Example 38 discloses the generation of a transgenic mouse that contains a transgene as recited in claim 57. As discussed in Example 38, a mouse strain containing five human light chain Vκ segments (KCo5-9272) was made by co-injection of YAC clone 4x17E1, which carries at least 32 different Vk segments, and the KC1B and KV4 transgenes. These two transgenes are described further in Example 21 (particularly pages 170-172), which states that KV4 contains 4 functional Vk segments and KC1B contains a single functional Vk segment, all 5 human Jk segments, the human intronic enhancer, human Ck and the human 3' kappa enhancer. The expression of the five Vk segments in the KCo5-9272 strain is demonstrated in Table 15 of Example 38.

Claim 64 has been similarly amended to recite a transgenic mouse comprising in its genome a human kappa light chain immunoglobulin transgene, where the transgene contains five human light chain Vκ segments, a plurality of human light chain Jκ segments, and a human light chain Cκ segment, which segments are operably linked to transcription regulatory sequences and undergo rearrangement in B lymphocytes *in vivo* to produce a repertoire of rearranged transgenes encoding a plurality of human kappa light chain polypeptides, which human kappa light chain polypeptides are produced in the transgenic mouse and where the transgenic mouse further comprises a human heavy chain immunoglobulin transgene that produces a repertoire of human heavy chain polypeptides that pair with the kappa light chain polypeptides to form a repertoire of human immunoglobulins in the mouse. As discussed above for amended claim 57, support for the amendments to claim 64 can be found in Example 38, beginning on page 236, line 35, of the specification. Additional support is found in Example 39, beginning on page 244, line 26. Example 39 discloses the production of a repertoire of human immunoglobulins from the KCo5-9272 mouse strain.

No new matter is added by these claim amendments. Applicant respectfully requests entry of the claim amendments.

Specification

Per the Examiner's request, a copy of pages 136-140 of the specification is submitted with this Response. Applicant asserts that no new matter is added through the submission as the pages were filed in the parent application, which is incorporated by reference into the present specification.

Double Patenting

U.S. Patent 5,625,126

The Examiner rejected claims 57-58, 62-65, 69-73 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-3 of U.S. Patent 5,625,126. Claims 58, 62-63, 65, 69-70 and 72-73 have been canceled in this Amendment. Applicant traverses the double-patenting rejections as it applies to pending claims 57, 64, and 71.

A double patenting rejection is proper when the claimed invention in an application is an obvious variation of the invention defined in a claim of a patent. MPEP §804. A double patenting rejection of the obviousness-type is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent principally underlying the double patenting rejection is not considered prior art. In re Braithwaite, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. In re Braat, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). MPEP §804.

Claim 57 has been amended to recite a transgenic mouse comprising in its genome a human kappa light chain immunoglobulin transgene, where the transgene contains five human light chain Vκ segments, a plurality of human light chain Jκ segments, and a human light chain Cκ segment, which segments are operably linked to transcription regulatory sequences and

undergo rearrangement in B lymphocytes *in vivo* to produce a repertoire of rearranged transgenes encoding a plurality of human kappa light chain polypeptides, which human kappa light chain polypeptides are produced in the transgenic mouse. Thus the mouse of claim 57 possesses five human light chain Vk segments.

Claims 2-3 of the '126 patent do not recite a mouse comprising in its genome a human light chain transgene that contains five human light chain Vκ segments. Claims 2-3 of the '126 patent also do not suggest every element of claim 57. Thus, the invention of claim 57 is not an obvious variation of the invention of claims 2-3 of the '126 patent. There is no motivation presented in the '126 patent to make a mouse as described in claim 57. Importantly, the mouse of claim 57 contains unexpected and beneficial properties over mice that contain other than five human light chain Vk segments. For example, as shown in Example 38 of the present specification, the KCo5-9272 mouse strain (KCo5 mouse) which possesses the transgene comprising five human light chain Vk segments, has approximately three-fold the fraction of B cells in the bone marrow as a transgenic mouse which possesses the transgene comprising four human light chain Vk segments (KCo4 mouse). Additionally, the pre-B cell population is also higher in the KCo5 mouse (9% as compared to 5% for the KCo4 mouse). The pro-B compartment of the KCo5 mouse is also elevated compared to the KCo4 mouse (11% for KCo5 as compared to 5% for KCo4).

As in claim 57, claim 64 has been amended to recite a transgenic mouse comprising in its genome a human kappa light chain immunoglobulin transgene, where the transgene contains five human light chain Vκ segments, a plurality of human light chain Jκ segments, and a human light chain Cκ segment, which segments are operably linked to transcription regulatory sequences and undergo rearrangement in B lymphocytes *in vivo* to produce a repertoire of rearranged transgenes encoding a plurality of human kappa light chain polypeptides, which human kappa light chain polypeptides are produced in said transgenic mouse. The mouse of claim 64 further comprises a human heavy chain immunoglobulin transgene that produces a repertoire of human heavy chain polypeptides that pair with the kappa light chain polypeptides to form a repertoire of human immunoglobulins in the mouse.

As set forth above in the discussion of claim 57, claim 64 (and dependent claim 71) is not obvious in view of claims 2-3 of the '126 patent. Claims 2-3 of the '126 patent do not recite or suggest a mouse comprising in its genome a human light chain transgene that contains five human light chain Vκ segments. Thus, the inventions of claim 64 and claim 71 are not obvious variations of the invention of claims 2-3 of the '126 patent. There is no motivation presented in the '126 patent to generate the mouse of claim 64 or 71. Nor is there any expectation that the mouse of claim 64 or 71 would possess such unique properties such as an increase in the fraction of B cells in the bone marrow, an increase in the pre-B cell population and an elevated pro-B compartment when compared to mice that contain other than five human light chain Vk segments.

The invention as described in the claims of the present application therefore is not an obvious variation of claims 2-3 of the '126 patent. As such, allowance of the claims of the present application would not unjustly extend the term of the '126 patent. Applicant respectfully asserts that the obviousness-type double patenting rejection as applied to claims 56, 64, and 71 in view of claims 2-3 of the '126 patent is improper and should be withdrawn.

U.S. Patent 5,789,650

The Examiner rejected claims 57-58, 62-65, and 69-73 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 5 of U.S. Patent 5,789,650. Claims 58, 62-63, 65, 69-70, and 72-73 have been canceled in this Amendment. Applicant traverses the double-patenting rejections as it applies to pending claims 57, 64, and 71.

For the same reasons as set forth above in the discussion regarding the double-patenting rejection in view of claims 2-3 of the '126 patent, claims 57, 64, and 71 are not obvious in view of claim 5 of the '650 patent. Claim 5 of the '650 patent does not recite a mouse comprising in its genome a human light chain transgene that contains five human light chain Vκ segments. Claim 5 also does not suggest every element of claims 57, 64 and 71. Thus, the inventions of claims 57, 64, and 71 are not obvious variations of the invention of claims 2-3 of the '650 patent. There is no motivation presented in the '650 patent to generate the mouse of claims 57, 64, or 71.

Nor is there any expectation that the mouse of claims 57, 64 or 71, would possess such unique properties such as an increase in the fraction of B cells in the bone marrow, an increase in the pre-B cell population, and an elevated pro-B compartment when compared to mice that contain other than five human light chain Vk segments.

The invention as described in the claims of the present application therefore is not an obvious variation of claim 5 of the '650 patent. As such, allowance of the claims of the present application would not unjustly extend the term of the '650 patent. Applicant respectfully asserts that the obviousness-type double patenting rejection as applied to claims 56, 64, and 71, in view of claim 5 of the '650 patent is improper and should be withdrawn.

U.S. Patent 5,877,397

The Examiner rejected claims 57-58, 61-65, and 68-73 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent 5,877,397. Claims 58, 62-63, 65, 69-70, and 72-73 have been canceled in this Amendment. Applicant traverses the double-patenting rejections as it applies to pending claims 57, 61, 64, 68, and 71.

For the same reasons as set forth above in the discussion regarding the double-patenting rejection in view of claims 2-3 of the '126 patent and claim 5 of the '650 patent, claims 57, 61, 64, 68, and 71 are not obvious in view of claims 1-10 of the '397 patent.

Claims 1-10 of the '397 patent do not recite a mouse comprising in its genome a human light chain transgene that contains five human light chain Vκ segments. Claims 1-10 of the '397 patent also do not suggest every element of pending claims 57, 61, 64, 68, and 71. Thus the invention of claims 57, 61, 64, 68, and 71 are not obvious variations of the invention of claims 1-10 of the '397 patent. There is no motivation presented in the '397 patent to generate the mouse of claims 57, 61, 64, 68, and 71. Nor is there expectation that the mouse of claims 57, 61, 64, 68, and 71 would possess such unique properties such as an increase in the fraction of B cells in the

bone marrow, an increase in the pre-B cell population, and an elevated pro-B compartment when compared to mice that contain other than five human light chain Vk segments.

The invention as described in the claims of the present application therefore is not an obvious variation of claims 1-10 of the '397 patent. As such, allowance of the claims of the present application would not unjustly extend the term of the '397 patent. Applicant respectfully asserts that the obviousness-type double patenting rejection as applied to claims 57, 61, 64, 68, and 71 in view of claims 1-10 of the '397 patent is improper and should be withdrawn.

35 U.S.C. §112, first paragraph

The Examiner rejected claims 57-62, 64-69, and 71-75 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of skill in the art to which it pertains to make or use the invention. The Examiner asserts that it would require undue experimentation to obtain and use a transgene encoding any fragment of the unrearranged germline kappa or lambda loci comprising the J regions and C gene operably linked to any or all V segment genes to make a transgenic animal of the present invention. Claims 58, 62-63, 65, 69-70, and 72-73 have been canceled in this Amendment. Applicant respectfully traverses this rejection and asserts that it does not apply to the currently pending claims 57, 61, 64, 68, and 71.

The Examiner asserts that the specification does not provide an enabling disclosure for making or using transgenes comprising the entire human Ig light chain loci. In the interest of expediting prosecution and without admitting the propriety of the rejection, Applicant has amended the claims to recite that the light chain transgene contains five Vk segments. All independent claims (*i.e.*, claims 57 and 64) now recite this requirement. Since the entire human Ig light chain locus contains more than five Vk segments, the Examiner's comment does not pertain to the claims as currently pending.

The Examiner further asserts that the specification fails to provide any guidance for genomic sequences encoding V, J, or C region genes of the lambda locus. In the interest of expediting prosecution and without admitting to the propriety of the rejection, Applicant has

amended the claims to recite that the light chain transgene is a "kappa" light chain transgene. Specifically, claim 57 has been amended to insert the term "kappa" prior to the instances of "light chain" and the terms V, J and C have been replaced with the kappa chain specific terms Vκ, Jκ, and Cκ. Similar amendments were made to claims 61, 64, 66, and 68.

The Examiner, in support of the 35 U.S.C. §112, first paragraph rejection, also asserts that the specification provides only one example (pKC2) of a kappa light chain locus which comprises more than one human kappa light chain V gene and fails to provide sufficient guidance for transgenes, YACs, or other gene constructs encoding distal V genes. Applicant respectfully disagrees. The specification provides numerous examples of transgenes and YACs used to create human kappa light chain loci. As pointed out by the Examiner, the specification teaches how to make the pKC2 gene which comprises 2 V kappa light chain genes. The specification, in Example 36, also teaches the human light chain transgene, KCo4 (depicted in Fig. 56). KCo4 comprises 4 functional Vκ segments, 5J segments, the Cκ exon, and both the intronic and downstream enhancer elements. The KCo4 transgene was generated by coinjecting two transgenes that can integrate into the genomic DNA as a contiguous 43kb transgene via homologous recombination. The specification further teaches the human light chain transgene KCo5, which contains all the segments of KCo4 with additional V segments introduced via a YAC (Example 38).

As amended, the claims recite a human kappa light chain immunoglobulin transgene where the transgene contains five Vk segments. The specification provides sufficient guidance to allow one of skill in the art to make a mouse containing the transgene recited in claims 57, 61, 64, 68, and 71. Specifically, guidance for generating a kappa light chain locus that contain five Vk segments, as recited in the claims, is provided in Example 38. Example 38 teaches the successful introduction into the mouse genome of functional human light chain V segments by co-injection of a human κ light chain minilocus and a YAC clone comprising multiple human Vκ segments. Specifically, Example 38 teaches how to use both transgenes and YACs to generate human kappa light chain loci containing a plurality of human light chain Vκ genes, a plurality of human light chain Jκ genes, and a human light chain Cκ gene. The YACs in Example 38 comprise Vκ genes that include sequences from the distal Vk region. The mouse strain in Example 38 was made by co-injection of YAC clone 4x17E1, which carries at least 32 different

Vk segments, and the KC1B and KV4 transgenes. These two transgenes are described further in Example 21, which states that KV4 contains 4 functional Vκ segments and KC1B contains a single functional Vk segment, all 5 human Jk segments, the human intronic enhancer, human Ck and the human 3' kappa enhancer. The expression of five Vκ segments in the KCo5-9272 strain is demonstrated in Table 15 of Example 38. The KCo5-9272 mouse strain (KCo5 mouse) generated by the procedure of Example 38 is shown to produce high affinity human antibodies (Examples 39 and 40).

The components that went into the KCo5 transgene of Example 38 can be used to make other transgenes having a different complement of 5 Vκ segments. For example, the YAC used to generate the KCo5 transgene contains at least 32 Vκ segments and can be coinjected with other transgenes disclosed in the specification to create other recombined transgenes.

The Examiner further asserts that the specification is not enabling for producing any transgenic animal other than a transgenic mouse. In the interest of expediting prosecution and without admitting to the propriety of the rejection, Applicant has amended the claims to be limited to a transgenic mouse. Specifically, claims 57, 59, 60, 61, 64, 66, 67, 68, and 71 have been amended to replace the term "non-human animal" with "mouse".

Applicant asserts that the pending claims are in compliance with 35 U.S.C. §112, first paragraph.

35 U.S.C. §112, second paragraph

The Examiner rejected claims 64-71 under 35 U.S.C. §112, second paragraph, as being incomplete for omitting essential elements. Claims 65 and 69-70 have been canceled through this Amendment. Independent claim 64 has been amended to recite a mouse that further comprises a human heavy chain immunoglobulin transgene. Applicant submits that amended claim 64, and claims 66-68 and 71 that depend thereon, are in compliance with 35 U.S.C. §112, second paragraph.

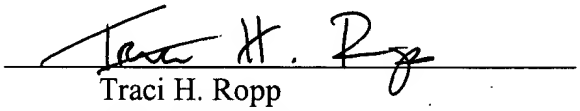
CONCLUSION

Applicant respectfully submits that the claims are now in condition for allowance. If upon, review, the Examiner feels there are additional outstanding issues, the Examiner is invited to direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,

DORSEY & WHITNEY LLP

Date: January 26, 2004



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